MAGNETIC RESONANCE

by GEORGE E. PAKE

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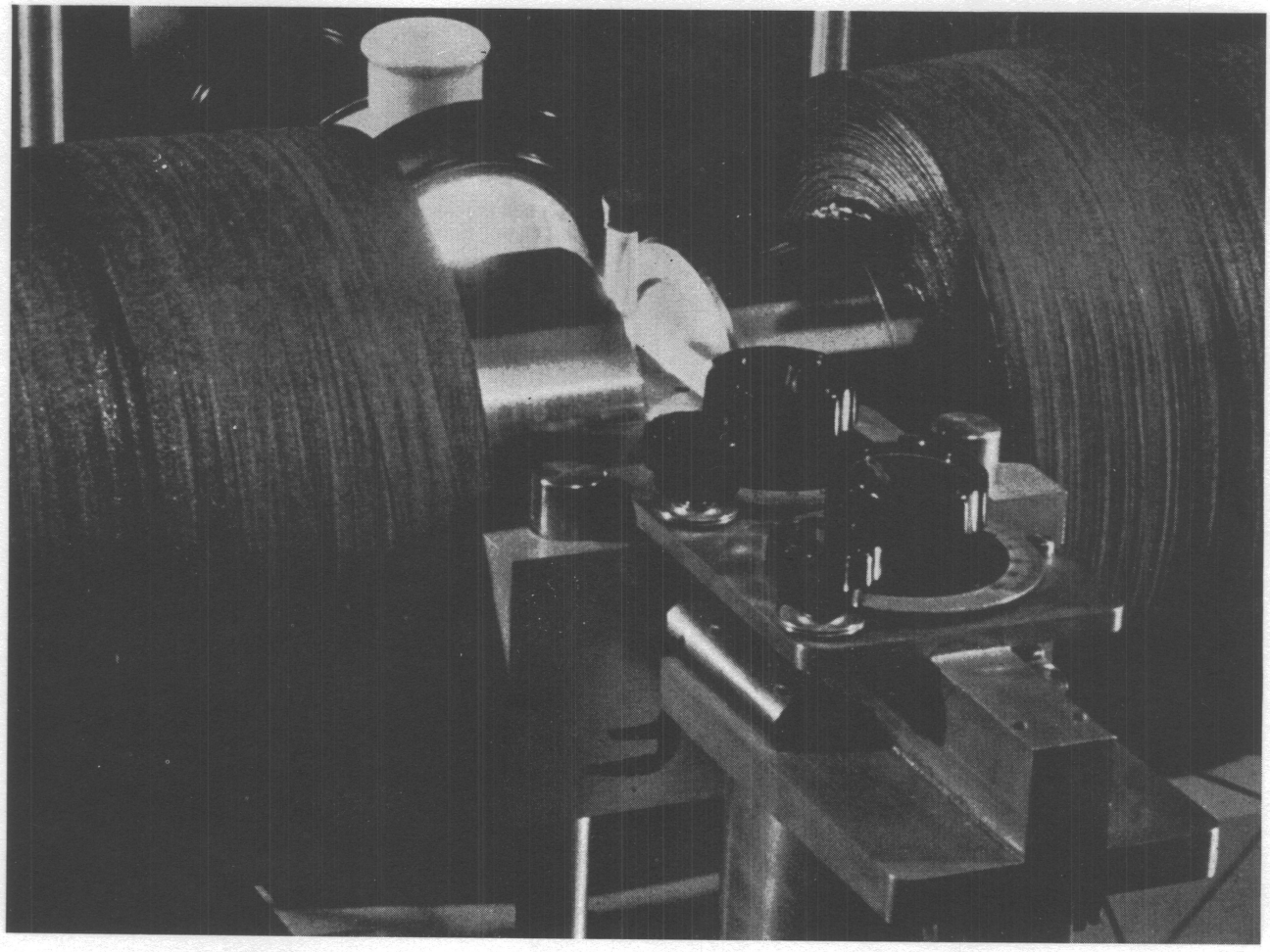
MAGNETIC RESONANCE

Atomic nuclei and electrons, which spin on their axes like tops, can be tipped over by magnetic fields. The technique furnishes much information about complex molecules and chemical reactions

by George E. Pake

Early in 1946 Edward Purcell at Harvard University and Felix Bloch at Stanford University announced, almost simultaneously, an interesting discovery in physics. They had found a way to tune in on the magnetic fields of the spinning nuclei of atoms. The work was important enough to win the 1952 Nobel prize in physics for Purcell and Bloch.

It is doubtful that many people outside the field of nuclear physics were much excited by or even took notice of these experiments at the time they were announced. But by now the phenomenon in question, called magnetic resonance, has become a matter of very wide interest indeed. Scientists in various distantly separated lines of work—geologists, chemists, biologists—are, if anything, even more excited about the discovery



MAGNETIC-RESONANCE EXPERIMENT on electrons in chlorophyll demonstrates that photosynthesis involves free radicals. The sample of chlorophyll is in the upright tube in the center, between the poles of the magnet. The light source which illuminates sample is behind magnet. This photograph was made in the laboratory of Barry Commoner at Washington University in Saint Louis.

than nuclear physicists. For it has led unexpectedly to the development of a sensitive tool useful for a multitude of purposes, from prospecting for minerals in the earth to analyzing the chemistry of living organisms.

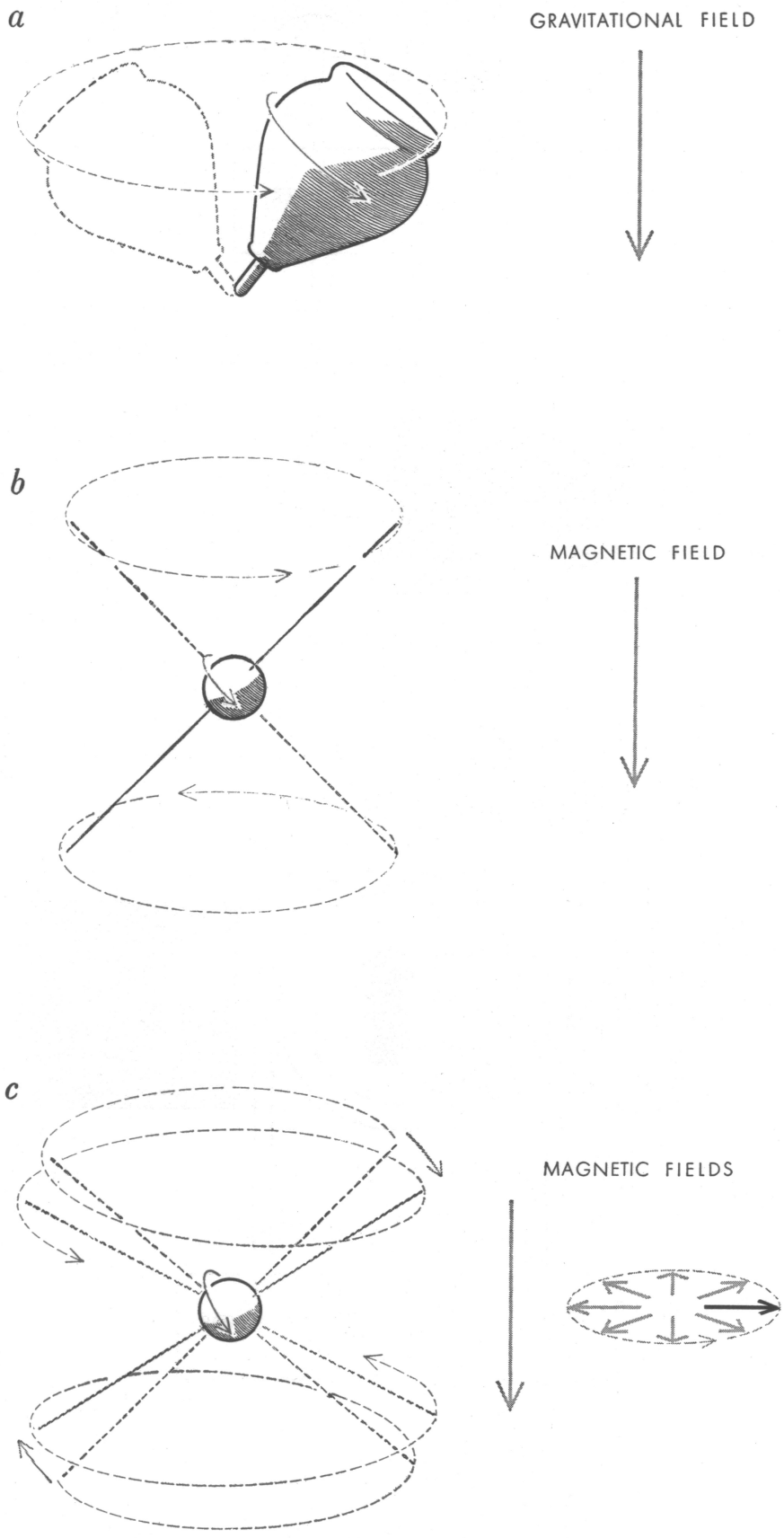
We must start this story by giving thought, as Purcell and Bloch did, to the spinning behavior of the proton. Like the rotating earth, a proton constantly spins around its axis (as do all the other elementary particles of the atom). It spins eternally with a certain momentum, reckoned in the proton's case as one-half unit. Since the proton carries an electric charge, its spin generates a magnetic field; in other words, the proton is a tiny magnet. Now we can ask ourselves the intriguing question: What will happen if we apply an outside magnetic field to this little magnet? Purcell and Bloch fell to wondering (independently) whether it would be possible to use a magnetic field to manipulate the spinning protons in a piece of matter: say, flip them over so that their north and south poles were reversed.

Here it is useful to think of an ordinary spinning top or a gyroscope. As everyone knows, a gyroscope tipped from the vertical does not fall down; instead its upper end circles slowly (precesses) around the vertical. That is to say, the downward gravitational pull of the earth acts to swing the axis of the spinning gyroscope around rather than to tip it further. Similarly, if we apply magnetic force to a spinning proton it will make the proton precess, not tip over. Brute force, in the form of stepping up the strength of the magnetic field, will avail us nothing: it will merely cause the proton to precess faster.

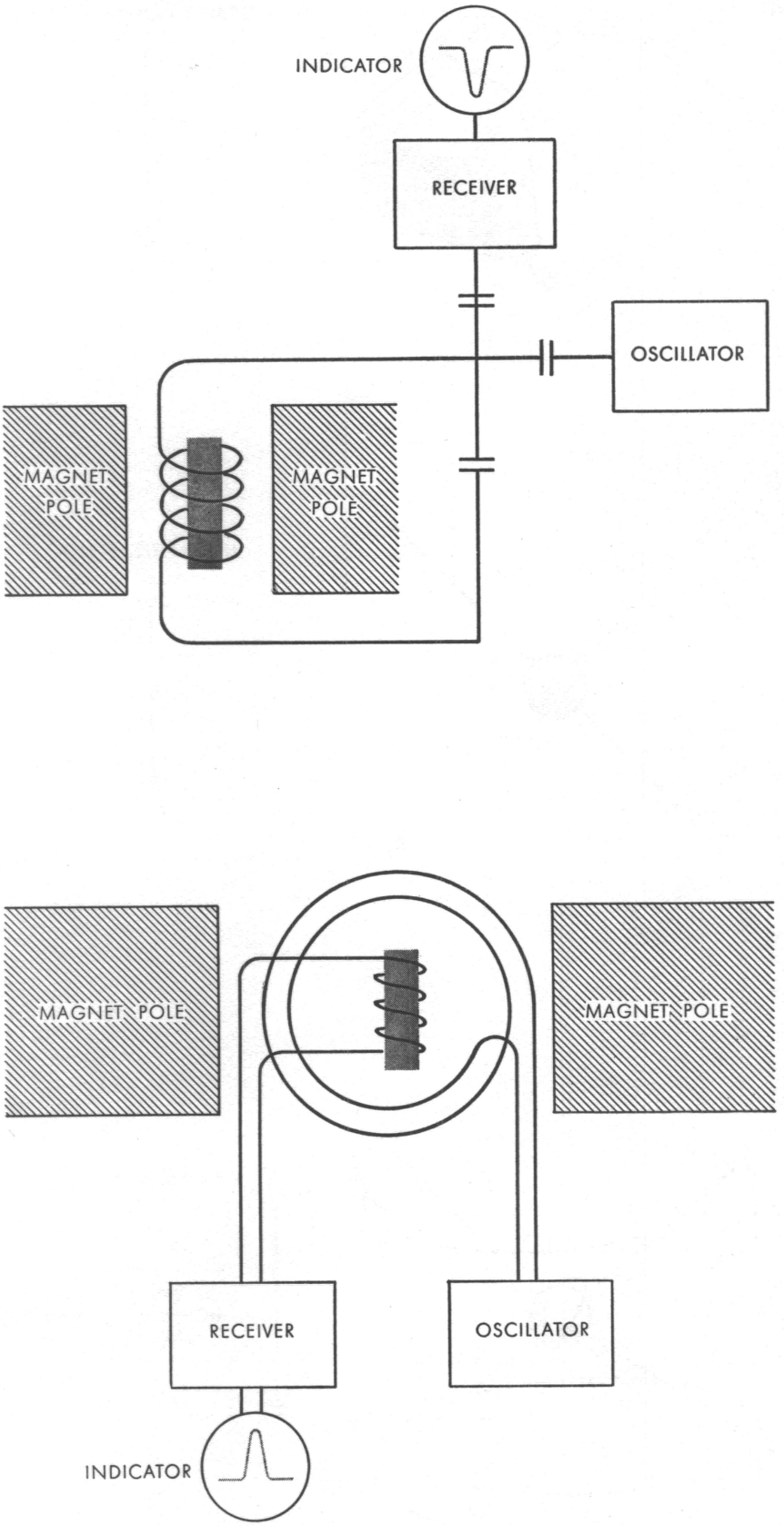
But there is a way to outwit the spinning particles. Suppose we apply a second magnetic field at right angles to the main field. Theory says that if we make the second field rotate around the first (by means of an alternating electric current in a coil), and if we time the rotation so that it coincides exactly with the rate of the proton's precession, we should be able to tip the proton over. In short, with proper tuning (at radio frequencies) the feat may be achieved by a magnetic-resonance effect.

A New Spectroscopy

The problem, then, was to find the resonance frequency and to detect the effect on the protons. Purcell and Bloch employed different methods to look for the effect. In Purcell's apparatus the sample of matter was placed between



GYROSCOPIC ACTION of a spinning top or particle causes it to revolve or precess around a vertical field tending to tip it over. Particle can be tipped, as shown in the diagram at the bottom, by applying in addition a rotating horizontal magnetic field (*right*), which revolves at exactly the same rate as the axis of the precessing particle in the vertical magnetic field.



NUCLEAR-RESONANCE DEVICES designed by Edward Purcell and Felix Bloch are diagrammed schematically. In Purcell's arrangement (*top*) a single coil passes radio waves from oscillator into sample (*gray bar*) and feeds into receiver. Resonance is indicated by a dip in received energy. In Bloch's apparatus (*bottom*) a separate coil picks up energy from tipping particles. Resonance shows up as an increase in energy reaching the receiver.

the two poles of a magnet and surrounded with a coil which produced the second, rotating field [*see upper diagram at left*]. When the frequency was just right, energy passing along the coil was absorbed by protons in the sample of matter as they flipped over; this absorption of energy was recorded by a sudden dip in the strength of the signal reaching a radio receiver. Bloch's group, on the other hand, devised an instrument which recorded the event by induction of a voltage. As the protons flipped over, the motion of their magnetic fields induced a voltage in a second coil, and this signal was registered on an oscilloscope [*see lower diagram at left*].

The electron, like the proton, is a charged particle; it, too, spins and has a magnetic field—far stronger than the proton's, because it spins much faster. The electron also exhibits magnetic resonance. Since it is a stronger magnet and much lighter than the proton, it precesses much more rapidly in a given magnetic field. Whereas the proton is probed with radio waves in the range of a few megacycles per second (near the frequencies of ordinary home radio), for electrons the frequencies employed are in the microwave range, around 10,000 megacycles per second.

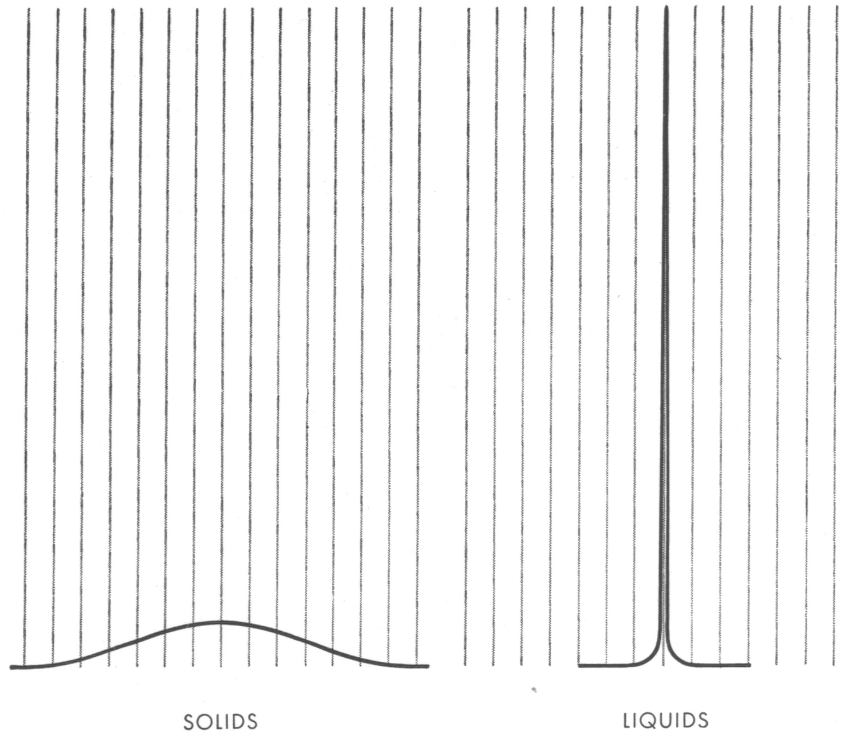
The magnetic resonance of protons and electrons makes it possible to learn many things about atomic nuclei, atoms and molecules. The magnetic probe amounts, in effect, to a new kind of spectroscopy. This brings us to the varied uses of the discovery in chemistry and biology.

The Structure of Molecules

Let us look, for example, at an organic compound such as cyclohexane (C_6H_{12}). We shall examine its resonance spectrum by means of nuclear magnetic resonance (NMR). We measure the substance's resonance in terms of the precession speed at which the nuclei flip over. That is, instead of tuning in to the resonance by varying the frequency of the rotating magnetic field, we use a fixed frequency and vary the strength of the main magnetic field, which controls the precession speed; when the nuclei flip, the resonance reading is taken as the strength of the magnetic field at that point (measured in gauss or oersteds).

When we subject a sample of cyclohexane at room temperature to the proper magnetic field, we get a sharp resonance reading. The compound's hydrogen nuclei flip simultaneously at a certain field strength (the carbon atoms are not

affected). Now the sharpness of this response has to be explained. In any collection of atoms we must reckon not only with the applied magnetic field but also with the little nuclear magnets of the atoms themselves. Each nucleus is subject to the magnets of its neighbors as well as to the applied field. The total magnetic field acting on a nucleus must vary from place to place in the material, because of the varying orientation of the nuclear magnets that happen to surround it. As a result of these variations, the responses to the external field should vary: it should take a slightly stronger applied field to flip some nuclei than others. This means that the resonance range for the whole group of nuclei should be a broad band rather than a sharp line. However, in a liquid the local variations are so short-lived, because of the rapid random motions and mixing of the molecules, that in effect all the nuclei are subject to about the same average field. Thus cyclohexane, a liquid at room temperature, gives a sharp magnetic-resonance line.

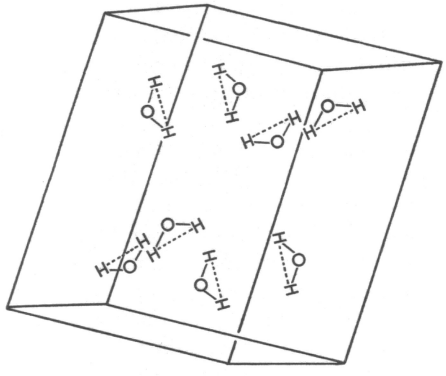


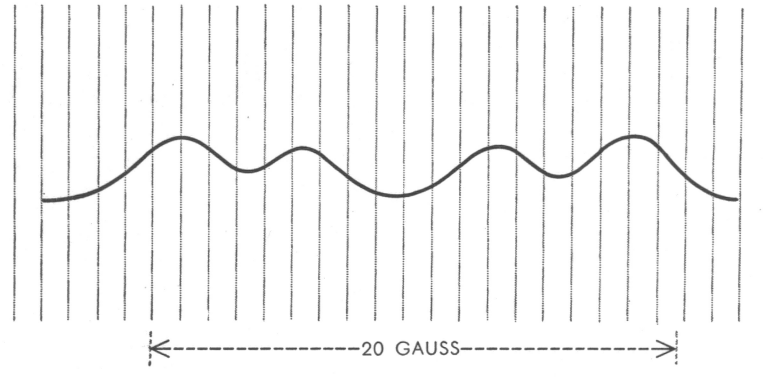
NUCLEAR-RESONANCE CURVES are broad for solids, narrow for liquids. The difference is actually greater than indicated here: the ratio of widths may be as great as 100,000 to 1.

The situation is different in a solid. Because the molecules occupy fixed positions, there are persisting local differences in the magnetic field, and accordingly solids tend to have a broad resonance. The resonance band may be as wide as 20 gauss, as against a sharp line as narrow as one 10,000th of a gauss for some liquids. But here cyclohexane offers an unusual and illuminating case. When it is frozen to the solid state, it still has a sharp resonance down to a temperature of 90 degrees centigrade below its freezing point. This tells us that the molecules in the solid must be in some kind of motion. Evidently they rotate around their positions in the crystal lattice, so that the magnetic field averages out to uniformity.

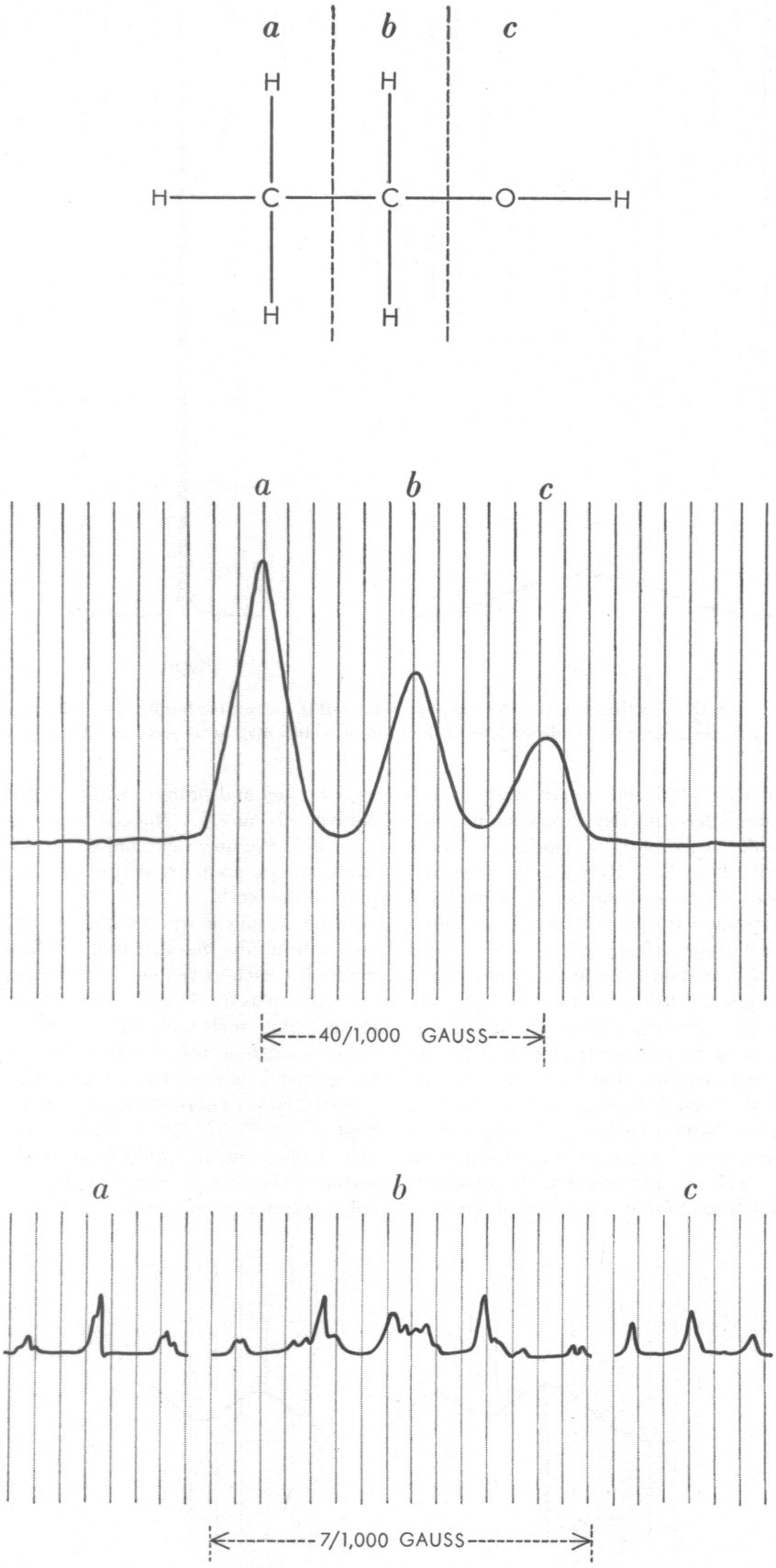
More detailed study of various substances, solid and liquid, leads to still more interesting developments. In 1947, while working as a graduate student with Purcell at Harvard, I found that the resonance of the hydrogen nuclei in gypsum was split into four distinct lines [*see chart below*]. Clearly these must reflect certain definite variations of the magnetic field within the gypsum crystal. By a theoretical analysis it was possible to translate the information into a picture of how the hydrogen atoms lie in the crystal structure. Here, then, was a new tool for analyzing the structure of crystals—a supplement to probing them with X-rays and neutrons. It is particularly useful for locating light atoms such as hydrogen and lithium, which deflect X-rays only weakly. Nuclear magnetic resonance has now been applied to the study of crystals by scientists in many parts of the world.

From crystals it was a logical step to go on to study the structure of giant molecules, such as rubber, polyethylene and other plastics. One of the problems in analyzing such molecules is to find out how much of their structure is orderly, or crystalline [see "Giant Molecules," a special issue of SCIENTIFIC AMERICAN; September, 1957]. C. W. Wilson, III, one of my graduate students at Washington University in Saint Louis, was able to show that nuclear magnetic reso-





GYPSUM CRYSTAL contains molecules of water, indicated in drawing at left as H-O-H. From the shape of the nuclear magnetic resonance (NMR) spectrum of gypsum (*right*) the positions of the water molecules in the structure of the crystal can be calculated.



ETHYL ALCOHOL, whose chemical formula appears at top, has a three-peaked NMR spectrum (*center*) when examined with a uniform magnetic field. Letters match hydrogen atoms in various sections of the molecule with their corresponding resonance curves. With a still more uniform field the central part of each curve splits further, as shown at bottom.

nance could be used to examine the structure of these huge molecules.

Fingerprints of Molecules

It is in liquids rather than solids, however, that the technique of nuclear magnetic resonance has achieved its most important triumphs of structural analysis. As we have seen, liquids show sharp resonances, because the magnetic field through the material is almost completely uniform. But a few irregularities can be detected when a liquid compound is examined under a very uniform applied field. Under these circumstances it becomes possible to read the resonance spectrum as a "fingerprint" of the structure of the molecule.

For example, James Arnold and Martin Packard at Stanford University, working with an extremely uniform applied field, were able to resolve the resonance of the hydrogen nuclei in the ethyl alcohol molecule (CH_3CH_2OH) into three separate resonances [*see upper chart at left*]. These singled out the three different groups that make up the molecule: CH_3, CH_2 and OH. The explanation is that the hydrogen nuclei in the three groups respond differently to the applied magnetic field because of a shielding effect of the atoms' electrons. The electrons themselves show no magnetism, for in a molecular combination electrons usually are paired off so that each cancels its partner's magnetic field. But an applied magnetic field slightly alters the motions of electrons around their atomic nuclei; the induced motions of the electrons in turn produce weak magnetic fields opposed to the applied field; this "diamagnetism" partly shields the nuclei from the external field. The amount of shielding differs in the different groups of a molecule, and this explains why the hydrogen atoms in the three groups composing ethyl alcohol have different resonances.

With higher resolution (*i.e.*, under a still more uniformly controlled magnetic field) the magnetic spectrum of the ethyl alcohol molecule splits up into an amazing array of separate resonances [*see lower chart at left*]. The spectrum is a fingerprint of the molecule which not only identifies it but also tells much about its structure. Indeed, from such a fingerprint a chemist can sometimes predict the behavior of a molecule.

Chemists in all branches of their discipline are now busily employing nuclear magnetic resonance to unlock the secrets of structure of many kinds of substances, from soap and motor oil to the extremely

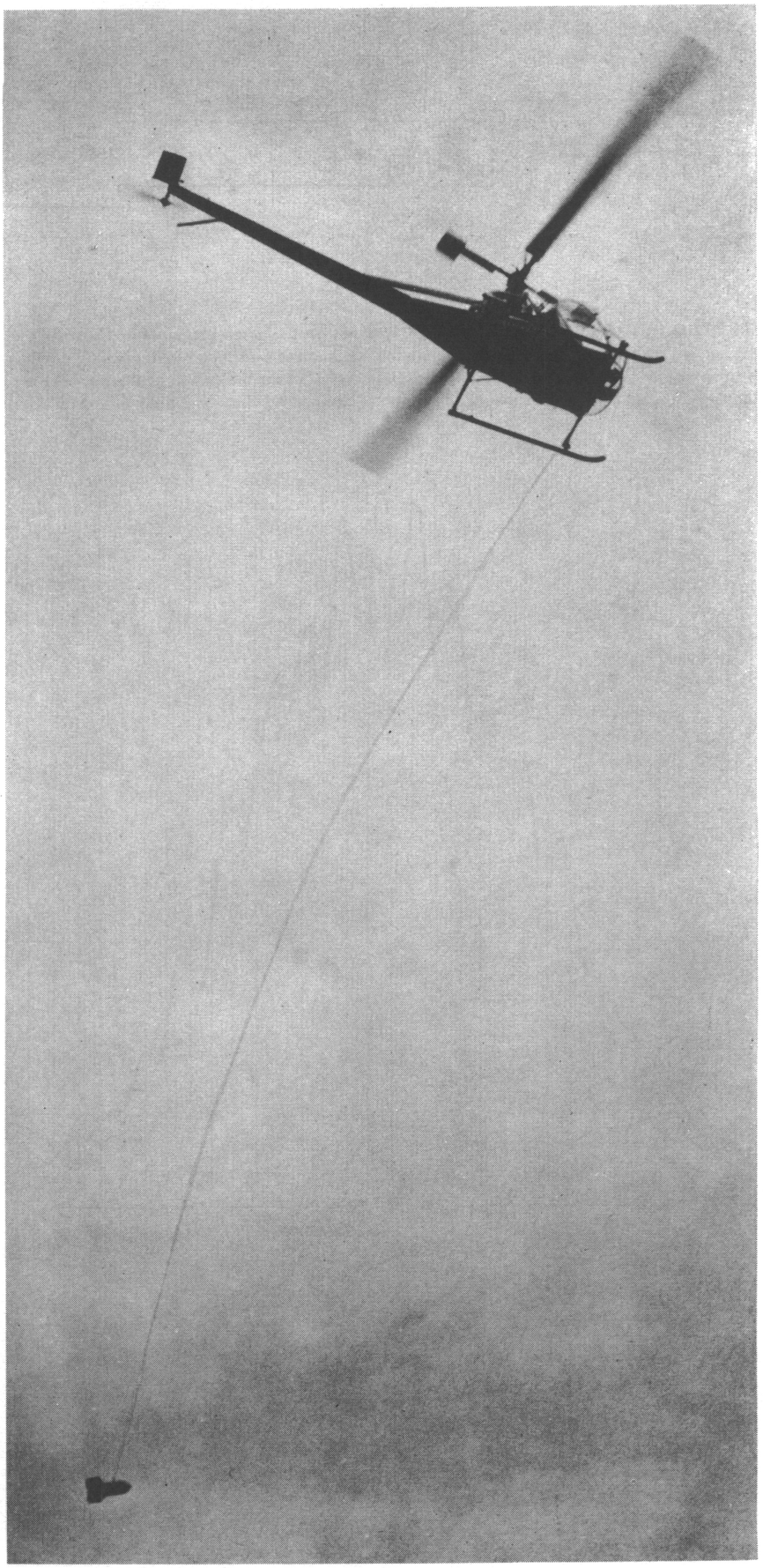
complicated molecules of living matter. One of the virtues of this new analytical tool is that it does not destroy the chemical under analysis. The chemist simply puts the sample in a coil, turns on the radio waves and the magnetic field, records the resonance spectrum and then takes out the sample intact.

Measuring the Earth's Field

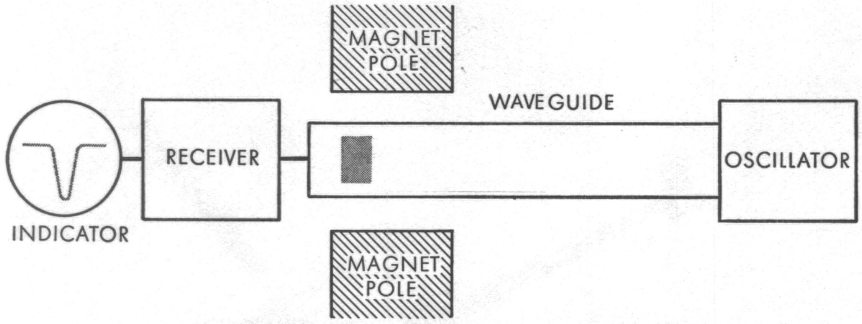
As a final illustration of the versatility of NMR let us look at a very different use—namely, exploring the earth's magnetic field. If very sharp precision in the strength of the applied field is needed to hit the resonance of a liquid, why not reverse the procedure and use resonance for precise measurement of magnetic fields? The difficulty about the earth's field is that it is extremely weak—only about half a gauss. To measure this by the resonance phenomenon, which previously had been studied in the laboratory with fields of thousands of gauss, posed quite a challenge. But Russell Varian and Packard, now with the Varian Associates, have solved the problem with an ingenious device.

Their instrument first lines up the protons in a sample of liquid with a moderately weak magnetic field. The protons are all oriented in one direction so that the whole sample, in effect, is a weak magnet. Then the polarizing field is suddenly switched off; the magnetic rug is pulled out from under the group of protons, so to speak. The nuclear magnets, which have been lined up in a direction *not* parallel to the earth's field, now begin to precess around the axis of this field. Their alignment rapidly breaks down, but in liquid benzene it lasts up to 20 seconds. This is long enough to measure the strength of the earth's magnetic field to an accuracy approaching one part in 10 million. The measurement is made simply by tuning in to the precession rate of the group of protons: since the earth's field produces the precession, the rate is a measure of the strength of the field.

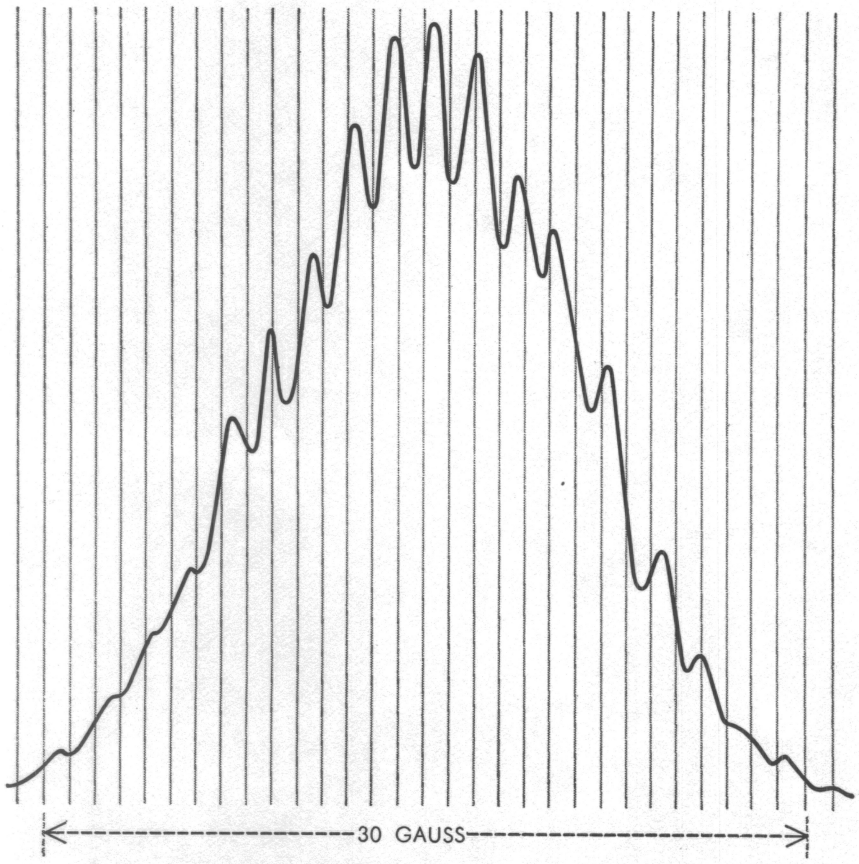
Varian and Packard named their instrument the proton precessional magnetometer. Obviously this amazingly sensitive device could serve to measure variations in the earth's magnetic field. It has already been put to use in prospecting for mineral deposits, from the air and on the ground [*see photograph at right*]. The instrument has also been shot in rockets to measure the strength of the earth's field at various heights above the surface. A magnetometer of this type is scheduled to go up in



MAGNETOMETER based on nuclear magnetic-resonance principle measures small variations in the earth's field. Here it is towed by a helicopter in a mineral-prospecting survey.



ELECTRON-RESONANCE APPARATUS operates on the same principle as Purcell's circuit shown on page 4. A microwave oscillator sends three-centimeter radio waves through the waveguide. The sample (*gray rectangle*) is mounted on the inside of the guide. Resonance is indicated by a decrease in the power delivered by the waveguide to the receiver.



HYPERFINE STRUCTURE (jagged splitting) of an electron-paramagnetic-resonance (EPR) spectrum indicates various positions of the unpaired electron in a free-radical molecule. This curve comes from naphthalene radicals. Gray dots in the structural outline of the radical at bottom indicate that the free electron wanders over many parts of the molecule.

one of the U. S. artificial satellites soon. Surely Purcell and Bloch could hardly have foreseen that their exploration of the magnetism of the proton would lead to such developments.

The Resonance of the Electron

Let us turn now to the magnetism of the electron. The magnetic resonance of this particle was discovered by a Soviet physicist, E. K. Zavoisky, in 1944, before Purcell and Bloch tuned in on the proton. But curiously enough the Russians apparently were not as quick to exploit the discovery as physicists in the U. S., Great Britain and the Netherlands. At all events, the electron's resonance, called electron paramagnetic resonance (EPR), has now been forged into a tool as important in its area of usefulness as nuclear magnetic resonance.

As we have seen, the electron, because of its smaller mass and faster spin, is a much stronger magnet than a proton. As a result, a given magnetic field makes it precess far more rapidly. Its precession rate in the standard laboratory magnetic field is in the range of the frequency of radio microwaves—that is, about 10,000 megacycles per second, or a wavelength of about three centimeters.

When microwaves travel down a rectangular waveguide (the tube used to conduct such waves), they produce a rotating magnetic field at any fixed point. This field can serve to flip over the electron magnets in matter, just as a rotating field in a coil flips protons. The experimenter may place the sample of material on a side wall of the waveguide, turn on the radio waves and apply an external magnetic field to make the electrons precess. When the precession rate reaches the resonance value and the electrons flip, they extract energy from the radio waves, and the reading on a receiver at the end of the tube dips accordingly.

Now this technique obviously can tell us nothing about substances in which the electrons are all paired, *i.e.*, where the electrons' magnetism is neutralized. But it has proved very helpful indeed in studying material with unpaired electrons. Electron resonance was first applied to investigate crystals containing elements with unfilled electron shells (therefore unpaired electrons)—elements such as manganese and iron. Much has been learned about substances of this kind, particularly about those used for "magnetic" cooling of matter to very low temperatures.

But more exciting has been the discovery that electron resonance can be used to investigate free radicals, the

transitory molecular fragments that play a crucial role in many chemical processes, including the chemical activities of living cells [see "Free Radicals," by Paul D. Bartlett; SCIENTIFIC AMERICAN, December, 1953]. Free radicals, of course, have unpaired electrons, and with the electron-resonance technique it is sometimes possible to detect these fleeting substances and to learn something about their structure and behavior.

At first thought one might suppose that the resonance spectrum of the unpaired electron in a free radical should always be the same—one free radical indistinguishable from another. But this is not the case. The electron is affected by the magnetic field of the nuclei in whose neighborhood it happens to be, and as the free electron wanders about in the molecular fragment, it is subjected to varying magnetic fields. As a result its resonance may be split into a "hyperfine structure" [*see chart on page 8*]. From the splitting we may learn where the electron spends its time and at what rate the free radical is likely to enter into chemical reactions.

Such studies are not limited to natural free radicals. With high-energy particles from an accelerator it is possible to break a molecule into fragments, and the fragments can sometimes be frozen in their tracks, so to speak, by keeping the sample at a very low temperature. We can then see what has happened to the molecule by examining the electron resonances of the fragments. This kind of investigation could be useful for studying the chemical effects of radiation on certain plastics; irradiation is known to strengthen some plastics by causing them to form new chemical bonds. Magnetic resonance also looks promising as a tool for investigating the free radicals that catalyze the synthesis of high polymers such as rubber or polyethylene [see "How Giant Molecules Are Made," by Giulio Natta; SCIENTIFIC AMERICAN, September, 1957].

Resonance in Living Cells

To illustrate the interest of biologists in magnetic resonance, I shall close this account with an episode that began in Saint Louis one evening in 1951. After attending a chamber music concert, a few members of the Washington University faculty repaired to someone's home for coffee, and the conversation turned (probably to the wives' chagrin) to shop talk. Barry Commoner of the botany department fell to discussing the theory that free radicals play an important role in the processes of oxidation and reduction in living cells, and he remarked how difficult it was to detect free radicals in living systems. I suggested that electron resonance might be helpful, and offered to help Commoner and his group learn how to use the method. Thus began a most interesting series of experiments.

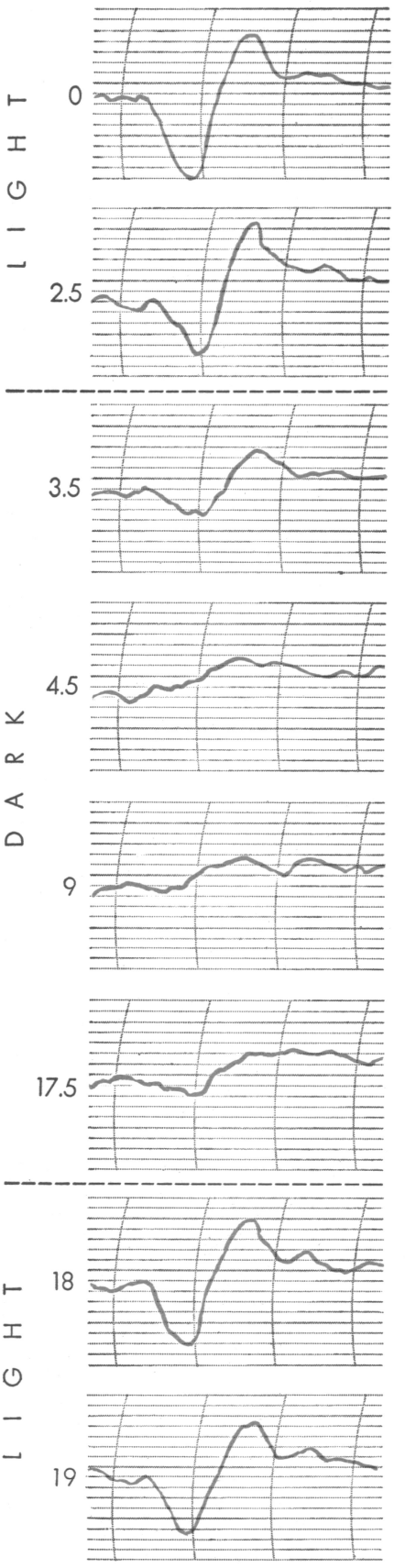
The first results were disappointing. Since the experiments involved cultures of cells (yeast and other organisms), there was moisture in the microwave apparatus, and moisture absorbs microwaves. This absorption of course masked the dip in radio energy produced by magnetic resonance. Even so, the experimenters finally detected a weak resonance from yeast and found that its intensity varied with the rate at which oxygen was consumed by the yeast cells. Then a resonance was discovered in green leaves ground up and quickly freeze-dried to eliminate the absorption by moisture.

To study the active process of photosynthesis in its necessary moist environment, however, called for a much more sensitive apparatus. Jonathan Townsend of the physics department succeeded in devising one, and it became possible to work with living cells. The cells selected contained chloroplasts—the small, green, chlorophyll-packed bodies which are thought to carry out most if not all the steps of photosynthesis.

The cells were placed in the sensitive magnetic resonance apparatus and were simultaneously irradiated with white light from a 50-candle-power lamp. The chloroplasts immediately showed a dramatic resonance spectrum [*see charts at right*]. When the light was turned off, the resonance soon weakened or disappeared entirely. Next the cells were exposed to light of various specific wavelengths; it turned out that the resonance appeared at the very same range of wavelengths of light that produces photosynthesis.

Commoner and Townsend have gone on to further experiments which not only have linked free-radical activity firmly to photosynthesis but have also indicated that free radicals are involved in the metabolism of cancer cells. And biological investigators in many other laboratories have begun to adopt electronic resonance as a tool in their researches.

That basic discoveries in science invariably bear fruits which cannot be foretold is an old story to scientists. Even so it has been a great thrill to see what has grown out of the work of Purcell, Bloch and Zavoisky, who were seeking only to get a better understanding of the magnetism of the particles in the atom.



CHLOROPHYLL SAMPLE gives sharp EPR spectrum when irradiated with light. This proves that free radicals are involved in photosynthesis. Numbers at left indicate minutes from the start of the experiment.

The Author

GEORGE E. PAKE was Edward Purcell's graduate student at Harvard University when Purcell was just beginning his Nobel-prize-winning work on magnetic resonance. Pake, who is now professor of physics at Stanford University, has been investigating magnetic resonance ever since. Pake grew up in Kent, Ohio, where his father taught English at Kent State University. As a student in the University's "laboratory" high school for teacher training, he had access to the University library, and there his interest soon turned from baseball and model airplanes to physical science. With the help of Kent State's faculty, Pake received a head start in physics which served him well when, as a Westinghouse Scholarship student at the Carnegie Institute of Technology, he received his B.S. and M.S. degrees just 32 months after matriculating. "My undergraduate career whizzed by in a kind of blur," Pake reports. "I often think I would never have survived the concentrated dose of studies had it not been for my music and the opportunity to play French horn in the Carnegie Tech orchestra." Pake worked at Westinghouse Research Laboratories for a year, then went to Harvard, where he received his Ph.D. in 1948. Four years later, at the age of 28, he became chairman of the physics department at Washington University in Saint Louis. He has been at Stanford since 1956.

Bibliography

NUCLEAR AND ELECTRONIC SPIN MAGNETIC RESONANCE. John E. Wertz in *Chemical Reviews,* Vol. 55, No. 5, pages 829-955; October, 1955.

NUCLEAR MAGNETIC RESONANCE. E. R. Andrew. Cambridge University Press, 1955.

NUCLEAR MAGNETIC RESONANCE. G. E. Pake in *Solid State Physics,* Vol. 2, pages 1-91; 1956.

NUCLEAR MAGNETISM IN RELATION TO PROBLEMS OF THE LIQUID AND SOLID STATES. E. M. Purcell in *Science,* Vol. 107, No. 2,783, pages 433-440; April 30, 1948.

SPECTROSCOPY AT RADIO AND MICROWAVE FREQUENCIES. D. J. E. Ingram. Butterworths Scientific Publications, 1955.